The Time for Continued Investments in Cancer Research Is Now

Currently an American Cancer Society Professor at Dartmouth Medical School, Ethan Dmitrovsky, M.D., was a fellow at NCI during the 1980s. During that time, he began the research that still defines his career today: using pharmacological agents to induce terminal differentiation in tumor cells for cancer therapy. This year, Dmitrovsky became chair of the NCI's prestigious Board of Scientific Counselors for Clinical Sciences and Epidemiology. In that capacity, he will guide efforts by this Board's 22 extramural member scientists from cancer centers and universities across the U.S. to advise NCI on future directions for intramural cancer research. Dr. Dmitrovsky graduated from Harvard College and Cornell University Medical College, and completed an internal medicine residency at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York. He was a faculty member at MSKCC for more than a decade prior to joining the Dartmouth faculty as the Andrew G. Wallace Professor and Chair of the Pharmacology and Toxicology Department.

I recall my fellowship at NCI as a transformational experience that allowed me to combine in-depth science in clinical trials with laboratory-based research. Ever since, I've been impressed with the public-spirited nature of NCI—and CCR in particular—and how its leadership is extraordinarily devoted to the prudent use of public funds to combat the daunting problem of cancer.

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Cancer Cell Differentiation

My interest in differentiation therapy began with a landmark publication from Charlotte Friend, M.D., at Mt. Sinai Hospital in New York. During the 1970s, she showed that dimethyl sulfoxide (DMSO) could trigger mouse leukemia cells to become terminally differentiated hemoglobin-producing cells that stopped growing. At NCI, I set out to identify what regulated that process.

My collaborators and I found that expression of the *c-myc* oncogene falls and rises precipitously following DMSO treatment, and we therefore hypothesized that *c-myc* might regulate differentiation. So, we set about engineering mouse erythroleukemia cells to over-express *c-myc*—the idea being that if we could block this fluctuation, we might prevent mouse leukemia cells from differentiation in response to DMSO. We confirmed this was the case, and published those findings in *Nature*. The finding was replicated by several other groups, leading to the conclusion that oncogenes can control a tumor cell's differentiation state.

But, as a clinician and a scientist, I didn't want to *prevent* tumor cells from differentiating; I wanted to do the opposite, and, from a clinical perspective, the DMSO dose needed to induce tumor cell differentiation in patients was too high. However, we also knew from the work of Theodore Breitman, M.D., at NCI, that all-trans-retinoic acid—a natural derivative of vitamin A—could induce maturation of acute promyelocytic leukemia (APL) cells at levels that are a thousand times lower than the millimolar doses needed with DMSO.

(Photo: Dartmouth Medical School)

Ethan Dmitrovsky, M.D.

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Moving Towards Retinoic Acid

This formed the basis for my decision to study retinoic acid in differentiation therapy. At around the same time, two research teams—one headed by Pierre Chambon, M.D., from INSERM, in Strasbourg, France, and another by Ronald Evans, Ph.D., from the Salk Institute in San Diego, Calif.—reported the discovery of retinoic acid receptors. I also became aware of a discovery from Chinese investigators showing that retinoic acid could produce remissions in APL patients. These findings led us to conduct the first U.S. clinical trial with retinoic acid in APL patients, which we reported in the *New England Journal of Medicine*. That trial produced two important findings: first, that retinoic acid could stimulate leukemia cell maturation; and second, that the patients who responded to the drug had an aberrant retinoic acid receptor.

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This was, in many ways, an early example of targeted therapy, and upon coming to Dartmouth, I decided to expand my research by investigating whether retinoic acid might function as a *preventative* agent in cancer. That research resulted in a paper, published in *Proceedings of the National Academy of Sciences*, showing that retinoic acid can prevent lung cancer *in vitro* via destruction of the G1 cyclins. A hallmark of retinoic acid response in all contexts is, therefore, G1 arrest. I set out to identify the precise mechanisms involved in that process, and launched a decade-long effort to determine if triggering the G1 arrest and subsequent cellular growth inhibition pathway could have clinical benefits for patients with lung cancer.

The Present and Beyond

Meanwhile, despite *in vitro* data suggesting the opposite, clinical trials have clearly shown that classic retinoids, carotenoids, and other vitamin A derivatives are unable to prevent lung cancer in patients. My research and that of other laboratories has shown that a specific retinoic acid receptor—the RAR-beta receptor—triggers G1 arrest. However, this receptor is often silenced in lung cancer and in the bronchial epithelial cells of smokers, which may explain in part why these clinical trials haven't been successful. RAR-beta partners with retinoid X receptor (RXR) to form a complex, and we've now shown *in vitro* that by targeting RXR with rexinoids, namely, bexarotene, it's possible to activate GI arrest by inducing degradation of G1 cyclin proteins. During the last 10 years, we've focused on this finding and have used bexarotene to engage the RXR pathway in cooperation with a second pathway that we are able to modulate with the epidermal growth factor receptor (EGFR) inhibitor erlotinib. By combining these two drugs, we broaden their pharmacological activity. Phase 0, Phase 1, and Phase 2 clinical data have since shown that they produce objective responses in lung cancer patients ***with*** k-ras mutations, and also in patients ***without*** "activating" EGFR mutations in their lung cancers. This work has now been independently replicated by a team at M.D. Anderson Cancer Center, and our future work continues to investigate the potential for this treatment regime in lung cancer.

I regard it as a privilege to care for patients who have life-altering medical conditions, and I take great pleasure in being a small part of the many research groups working tirelessly toward the creation and testing of better therapeutics. It's an honor to work with the Board of Scientific Counselors in its efforts to move new discoveries from NCI into the broader cancer-care enterprise. With new discoveries emerging on an almost daily basis from the human genome, the time is right for continued investments in cancer research, and especially for the translational work that brings revolutionary science from the bench to the bedside.

The NCI *is* the nation's cancer center, and so it is with a tremendous sense of responsibility that I look forward to continuing my work with the distinguished members of the Board, thus ensuring that NCI remains very squarely at the forefront of the nation's cancer research efforts.